

FORM PTO-1390
(REV 10-95)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. §371**

SCHUB 1

U.S. APPLICATION NO. (If known, see 37 CFR §1.5)

09/937302

INTERNATIONAL APPLICATION NO.

PCT/DE00/01028

INTERNATIONAL FILING DATE

31 MARCH 2000

PRIORITY DATE CLAIMED

31 MARCH 1999

TITLE OF INVENTION

PHARMACEUTICAL COMPOSITION WITH AN EXTRUSION ADDITIVE

APPLICANT(S) FOR DO/EO/US



HÜLSMANN, Stefan, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
 - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
 - ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

| | | | | | |
|--|--------------|---|---|-------------------------------------|--|
| U.S. APPLICATION NO. (if known, see 37 CFR §1.51) 09/937302 | | INTERNATIONAL APPLICATION NO. PCT/DE00/01028 | | ATTORNEY'S DOCKET NUMBER SCHUB 1 | |
| 17. <input checked="" type="checkbox"/> The following fees are submitted: BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)): Search Report has been prepared by the EPO or JPO..... \$860.00 International preliminary examination fee paid to USPTO (37 CFR §1.482)..... \$690.00 No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))..... \$710.00 Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO..... \$1000.00 International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... \$100.00 <div style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT = \$860.00</div> | | | | CALCULATIONS PTO USE ONLY | |
| | | | | | |
| Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 C.F.R. §1.492(e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30 | | | | | |
| CLAIMS | NUMBER FILED | NUMBER EXTRA | RATE | | |
| Total claims | 14 - 20 = | 0 | x \$ 18.00 | \$0.00 | |
| Independent claims | 2 - 3 = | 0 | x \$ 80.00 | \$0.00 | |
| MULTIPLE DEPENDENT CLAIM(S) (if applicable) | | | + \$ 270.00 | | |
| TOTAL OF ABOVE CALCULATIONS = | | | | \$860.00 | |
| Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28). | | | | | |
| SUBTOTAL = | | | | \$860.00 | |
| Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 C.F.R. §1.492(f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30 | | | | | |
| TOTAL NATIONAL FEE = | | | | \$860.00 | |
| Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). \$40.00 per property. | | | | | |
| TOTAL FEES ENCLOSED = | | | | \$860.00 | |
| | | | | Amount to be refunded: | |
| | | | | charged: | |
| a. <input checked="" type="checkbox"/> A check in the amount of <u>\$860.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>13-3402</u> in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>13-3402</u> . A duplicate copy of this sheet is enclosed. | | | | | |
| NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status. | | | | | |
| SEND ALL CORRESPONDENCE TO: Customer Number 23,599 | | | | | |
|  23599 PATENT TRADEMARK OFFICE | | |  SIGNATURE <u>Anthony J. Zelano</u> NAME <u>27,969</u> REGISTRATION NUMBER | | |
| Filed: 26 September 2001 | | | | | |
| AJZ:kmo | | | | | |

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No. : PCT/DE00/01028
International Filing Date : 31 MARCH 2000
Priority Date(s) Claimed : 31 MARCH 1999
Applicant(s) (DO/EO/US) : HULSMANN, Stefan, et al.

Title: PHARMACEUTICAL COMPOSITION WITH AN EXTRUSION ADDITIVE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

5. (Amended) Pharmaceutical composition according to Claim 1, wherein as an additional adjuvant, polyvinylpyrrolidone, polyethylene glycol or vinylpyrrolidone-vinyl acetate copolymer or a mixture that consists of the above-mentioned substances is contained.
6. (Amended) Pharmaceutical composition according to Claim 1, wherein the melt extrusion is carried out without additional heat input.
7. (Amended) Pharmaceutical composition according to claim 1 that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.
8. (Amended) Pharmaceutical composition according to claim 1 that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and glycerol tribehenate and joint melt extrusion at 60°C.
9. (Amended) Pharmaceutical composition according to claim 1 that can be obtained by mixing ethinylestradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.

12. (Amended) Process according to claim 10, wherein in addition, the extruded mixture is ground and further processed into pharmaceutical agents with additional pharmaceutically compatible adjuvants and additives.

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REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,

 Reg. #32,004

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants
MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza 1
2200 Clarendon Boulevard, Suite 1400
Arlington, VA 22201
Direct Dial: 703-812-5311
Facsimile: 703-243-6410
Email: zelano@mwzb.com

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 5-9 and 12 have been amended as follows:

5. (Amended) Pharmaceutical composition according to ~~at least one of the above~~ Claims 1, wherein as an additional adjuvant, polyvinylpyrrolidone, polyethylene glycol or vinylpyrrolidone-vinyl acetate copolymer or a mixture that consists of the above-mentioned substances is contained.

6. (Amended) Pharmaceutical composition according to ~~at least one of the above~~ Claims 1, wherein the melt extrusion is carried out without additional heat input.

7. (Amended) Pharmaceutical composition according to ~~at least one of claims 1 to 6~~ that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.

8. (Amended) Pharmaceutical composition according to ~~at least one of claims 1 to 6~~ that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and glycerol trihehenate and joint melt extrusion at 60°C.

9. (Amended) Pharmaceutical composition according to ~~at least one of claims 1 to 6~~ that can be obtained by mixing ethinylestradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.

12. (Amended) Process according to claim ~~10 or 11~~, wherein in addition, the extruded mixture is ground and further processed into pharmaceutical agents with additional pharmaceutically compatible adjuvants and additives.

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Pharmaceutical Composition with An Extrusion Additive

This invention relates to pharmaceutical compositions that can be obtained by mixing at least one active ingredient with at least one extrusion additive from the group of polyalcohols esterified with fatty acids and joint melt extrusion.

The melt extrusion is a process that is known for the production of pharmaceutical compositions. In this case, very different adjuvants are used in the prior art for the various fields of application.

The melt extrusion process can be used universally per se, whereby, on the one hand, premixtures, which then can be further processed into the desired dosage forms, can be produced, or the desired dosage forms can be obtained directly by subsequent or simultaneous shaping.

In WO-9625151, the use of low-substituted water-insoluble hydroxypropylmethyl celluloses as additives in the case of the melt extrusion is described, by which the release of active ingredients can be set specifically.

DE-OS-4418837 thus describes a melt extrusion process that is suitable only for low-melting pharmaceutical active ingredients. According to this process, granulates that can be made into tablets directly are obtained, which then are further processed into the desired dosage forms.

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In WO-9629061, a melt extrusion process for high-melting, ionic pharmaceutical active ingredients is described, in which the active ingredients are melt-extruded in their nonionic form together with a polymer and a salt.

The use of lipids in the production of solid dosage forms according to the melt extrusion process is also described in DE-OS-19531277. In this connection, the addition of lipids prevents the bonding of the mixture during the melt extrusion and subsequent form-calendering.

The known processes and preparations have, i.a., the drawback that a suitable or optimal extrusion process must be provided for almost any active ingredient. In this case, for example, what melting point the active ingredient has or whether it is in ionic form is to be noted.

To achieve an adequate release and "content uniformity" of low-dosed and poorly water-soluble active ingredients, a micronization can be performed. Micronized pharmaceutical substances have considerable drawbacks, however. In addition to the large amount of dust formed and the associated burden for the personnel, primarily a difficult handling based on air adsorption and relatively low densities can be mentioned. In addition, micronized pharmaceutical substances also often show the tendency to aggregate. Moreover, micronization is associated with high costs (devices, individual buildings).

Another process according to the prior art contains the use of organic solvents, whereby the pharmaceutical substance solution is sprayed on the adjuvants that are used. This has the

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drawback that the necessary drying results in a thermal stress of the active ingredients. Disadvantageous ecological results when organic solvents are used are also given.

The object of this invention is therefore to provide a pharmaceutical composition that overcomes the drawbacks of the prior art.

The subject of this invention is therefore a pharmaceutical composition that can be obtained by mixing at least one active ingredient with at least one extrusion additive from the group of polyalcohols esterified with fatty acids and joint melt extrusion.

According to the invention, it is preferred that the extrusion additive be a sugar fatty acid ester, polyethylene glycol fatty acid ester or a glycerol fatty acid ester.

In this case, it is also preferred that the polyalcohols be diols, glycols, glycerol, mono-, di- or oligosaccharides, sugar alcohols, sorbitol, inositol, pentaerythritol, trimethylolpropane or polymer compounds with several hydroxy groups, polyalkylene glycols, polyethylene glycols, polyether polyols and polyester polyols and that the fatty acids have 1 to 31 carbon atoms and be unbranched and/or branched and/or saturated and/or unsaturated.

According to the invention, pharmaceutical compositions are also preferred in which as an additional adjuvant, polyvinylpyrrolidone, polyethylene glycol or vinylpyrrolidone-vinyl acetate-copolymer or a mixture of the above-mentioned substances is contained.

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The extrusion additives have a low melting point and/or their mixing with the active ingredient reduces the melting point in such a way that during the extrusion, the mixture does not have to be additionally heated but rather the compacting pressure in the extruder is sufficient to ensure the necessary temperature increase. It is therefore preferred that the melt extrusion be carried out without additional heat input.

The production of the extrusion additives is known in the art. They can be obtained by esterification of fatty acids with polyalcohols according to processes that are known in the art.

For esterification, suitable fatty acids are especially saturated, unbranched fatty acids, such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, palmitic acid, margaric acid, stearic acid, nonadecanoic acid, arachidic acid, behenic acid, lignoceric acid, cerotic acid, melissic acid, or saturated, branched fatty acids, such as isobutyric acid, isovaleric acid, tuberculostearic acid, or unsaturated, unbranched fatty acids, such as acrylic acid, crotonic acid, palmitoleic acid, oleic acid, erucic acid, sorbic acid, linoleic acid, linolenic acid, elaeostearic acid, arachidonic acid, clupanodonic acid, docosahexaenoic acid.

For esterification, suitable polyols are organic compounds that contain at least two alcoholic hydroxy groups in the molecule, such as diols, glycols, glycerol, mono-, di- or oligosaccharides, such as glucose, galactose, mannose, fructose,

arabinose, xylose, ribose, 2-deoxyribose, cellobiose, maltose, lactose, saccharose, gentiobiose, melibiose, trehalose, turanose, stachyose, acarbose, sugar alcohols, such as, for example, sorbitol and inositol, pentaerythritol, trimethylolpropane or polymer compounds, such as polyalkylene glycols, polyethylene glycols, polyether polyols and polyester polyols.

Subjects of the invention are pharmaceutical compositions with almost any active ingredients. Suitable active ingredients are, for example:

Acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir, alprazolam, albumin, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclometasone, benserazide, benzalkonium hydroxide, benzocaine, benzoic acid, betamethasone, bezafibrate, biotin, biperiden, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefaclor, cefalexin, cefadroxil, cefazolin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime axetil, chloramphenicol, chlorhexidine, chloropheniramine, chlorthalidone, choline, ciclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, clozapine, codeine, colestyramine, cromoglycic acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan,

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dextropropoxyphene, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, diltiazem, diphenhydramine, dipyrindamole, dipyrone, disopyramide, domperidone, dopamine, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, eucalyptus globulus, famotidine, felodipine, fenofibrate, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gemfibrozil, gentamicin, ginkgo biloba, glibenclamide, glipizide, glycyrrhiza glabra, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazides, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, iohexol, iopamidole, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labetalol, lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, methyl dopa, methylprednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamins and minerals, nystatin, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nicardipine, nicergolines, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrendipine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptyline, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, pentoxifyllines, phenylephrine,

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phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazosin, prednisolone, propafenone, propranolol, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, selegiline, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, theophylline, thiamin, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, volic acid, zidovudine.

The pharmaceutical compositions according to the invention are solid dispersions that have a number of advantages per se. Such solid dispersions show, for example, an improved dissolution behavior, which is especially advantageous in the case of active ingredients that are sparingly soluble in aqueous media.

The pharmaceutical compositions according to the invention have a number of advantages. The composition has a high homogeneity, especially also for low-dosed active ingredients, whose content, for example, is less than 0.025% relative to the single dose. This is of major importance especially for low-dosed hormone preparations.

The active ingredients in the pharmaceutical compositions according to the invention also have a high "content uniformity," i.e., the deviation of the content of the single dose fluctuates only within lower limits. This is also of major advantage

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especially for low-dosed active ingredients. Pharmaceutical compositions according to the invention meet the boundary values that are required by the pharmacopeia (USP, Ph. Eur.).

Another advantage of the pharmaceutical compositions according to the invention is that the rate of solution in water of sparingly soluble active ingredients is significantly improved and a homogeneous distribution of the pharmaceutical substance is achieved without primarily treating the active ingredients.

The described invention thus represents an alternative, e.g., to micronization, whereby melt extrusion economically achieves the tasks set for it -- improving the rate of solution and achieving "content uniformity" -- in a single step.

Another advantage of the pharmaceutical compositions according to the invention is that the rate of solution of sparingly soluble active ingredients is significantly improved. Thus, such active ingredients can also be introduced into a preparation that again releases the active ingredient quickly and almost completely within a short time.

It is also advantageous if the mixture that is to be extruded already contains adjuvants that must no longer be added later as tablet adjuvants. Such extruded masses can then be further processed into tablets for example with a number of tablet adjuvants that is lower than the otherwise common number (e.g., elimination of lubricant).

It is also especially advantageous that thermolabile active ingredients in the pharmaceutical compositions according to the invention can also be processed. Since the extrusion additives

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are low-melting, if the additives are properly selected, external heating is often unnecessary. In any case, however, the procedure can be performed at low temperatures, for example 40 to 60°C.

Another subject of this invention is a process for the production of pharmaceutical compositions in which at least one active ingredient is mixed with at least one extrusion additive from the group of polyalcohols esterified with fatty acids, and the thus obtained mixture is then subjected to a common melt extrusion.

It is preferred according to the invention that the melt extrusion be carried out without heat input.

The amount of added extrusion additives is arbitrary per se. The optimal amount for the respective active ingredient is easy for one skilled in the art to determine with a few tests. The extrusion additives do not have any negative effects on the shelf life of the compositions, preparations and pharmaceutical agents that are produced with them. The extrusion additives are also well-tolerated since their degradation in the body (ester cleavage) results in not toxic, but rather generally physiological substances.

The pharmaceutical compositions that can be obtained according to the invention can be used directly as pharmaceutical agents. In this case, it may optionally be necessary to add additional pharmaceutically compatible adjuvants and additives to the mixture that consists of the active ingredients or the active ingredients with the extrusion additive or additives and then to

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subject this mixture to the melt extrusion. In this case, for example, form calenders can also be used to obtain the desired pharmaceutical agents.

Such pharmaceutical agents, however, can also be produced according to the invention in such a way that in addition the extruded mixture is ground and further processed into pharmaceutical agents with additional pharmaceutically compatible adjuvants and additives.

Subjects of this invention are thus also pharmaceutical agents that contain a pharmaceutical composition according to the invention together with other pharmaceutically compatible adjuvants and additives.

Another subject of this invention is also the use of polyalcohols that are esterified with fatty acids as extrusion additives for the production of pharmaceutical compositions according to the invention.

The following examples explain the invention:

Example 1:

Improvement of the Rate of Solution

Composition of a melt extrudate:

10% 17- β -estradiol (not micronized)

50% PVP

40% saccharose-monopalmitate

The components are mixed. This mixture is subjected to a melt extrusion in a screw-type extruder with a one-hole nozzle at an extrusion temperature of 60°C and a screw speed of 50 rpm.

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The rate of solution is determined using dissolution tests (according to USP apparatus II) in 900 ml of 0.1N hydrochloric acid at 37°C over a period of 60 minutes (speed 100 rpm) and compared to that of the pure active ingredient and a physical mixture (Fig. 1).

The determination of the content of 17- β -estradiol is carried out by HPLC. The detection is carried out by photometry at a wavelength of 242 nm.

Example 2:

Composition of a melt extrudate:

10% 17- β -estradiol (not micronized)

50% vinyl pyrrolidone-vinyl acetate-copolymer

40% mixture that consists of PEG esters and glycerol esters

Extrusion temperature: 50°C; screw speed: 50 rpm

Example 3:

Composition of a melt extrudate:

30% 17- β -estradiol (not micronized)

30% PEG 6000

40% saccharose monostearate and distearate

Extrusion temperature: 60°C; screw speed: 50 rpm

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Example 4:

Improvement of the Rate of Solution of a Single Dose that Can Be Administered

Composition of a melt extrudate:

30% 17- β -estradiol (not micronized)

30% PVP

40% saccharose-monopalmitate

Extrusion temperature: 60°C; screw speed: 50 rpm

The cooled melt extrudate is crushed and mixed in a mixer with tablet adjuvants.

Composition of a powder molding compound:

8.3% melt extrudate with 17- β -estradiol

45.6% microcrystalline cellulose

45.6% corn starch

0.5% magnesium stearate

80 mg tablets with an active ingredient dose of 2 mg are produced on a tablet press.

The release rate is determined according to USP23-monography for estradiol tablets (Fig. 2). The contents of the samples are determined by HPLC with a photometric detection at 242 nm.

The requirements of the pharmacopeia on estradiol tablets with respect to the release are met.

Example 5:

Use of a Lubricant as an Extrusion Additive

Composition of a melt extrudate:

30% 17- β -estradiol (not micronized)

30% PVP

40% glycerol tribehenate

Extrusion temperature: 60°C; screw speed: 50 rpm

In the case of a subsequent tablet-making, the addition of a lubricant is no longer necessary.

Example 6:

Achieving a Homogeneous Distribution of a Pharmaceutical Substance in a Vehicle ("Content Uniformity")

Composition of a melt extrudate:

10% ethinylestradiol (not micronized)

50% PVP

40% saccharose-monopalmitate

Extrusion temperature: 60°C; screw speed: 200 rpm

The study on "content uniformity" is carried out according to USP23. Tablets or solid dispersions at a dosage of 20 μ g in each case are studied. The examination of "content uniformity" is carried out using HPLC with a fluorimetric detection ($\text{Exc}\lambda = 281 \text{ nm}$; $\text{Em}\lambda = 305 \text{ nm}$).

The results correspond to the requirements of the USP. The variation coefficient in the examination on "content uniformity" lies significantly below the required 6%.

[Key to Figure 1:]

Comparison of the Rate of Solution of 17- β -E2 to That of
17- β -E2 That Consists of a Melt Extrudate and a Physical Mixture

[First box:]

Composition of the melt extrudate

and the physical mixture:

10% 17- β -E2

50% PVP

40% saccharose monopalmitate

[Second box:]

17- β -E2, untreated

melt-extruded solid

dispersion

physical mixture

17- β -E2 freigesetzt [%] = 17- β -E2, released [%]

[Key to Figure 2:]

Dissolution Test of a Tablet with a 17- β -E2-Melt Extrudate

According to USP23

[Box:]

Composition of the solid dispersion:

30% 17- β -E2

30% PVP

40% saccharose monopalmitate

17- β -E2 freigesetzt [%] = 17- β -E2, released [%]

REPLACEMENT PAGE (RULE 26)

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Claims

1. Pharmaceutical composition that can be obtained by mixing at least one active ingredient with at least one extrusion additive from the group of polyalcohols esterified with fatty acids and joint melt extrusion.

2. Pharmaceutical composition according to claim 1, characterized in that the extrusion additive is a sugar fatty acid ester, polyethylene glycol fatty acid ester or a glycerol fatty acid ester.

3. Pharmaceutical composition according to claim 1, wherein the polyalcohols are diols, glycols, glycerol, mono-, di- or oligosaccharides, sugar alcohols, sorbitol, inositol, pentaerythritol, trimethylolpropane or polymer compounds with several hydroxy groups, polyalkylene glycols, polyethylene glycols, polyether polyols and polyester polyols.

4. Pharmaceutical compositions according to claim 1, wherein the fatty acids have 1 to 31 carbon atoms and are unbranched and/or branched and/or saturated and/or unsaturated.

5. Pharmaceutical composition according to at least one of the above claims, wherein as an additional adjuvant, polyvinylpyrrolidone, polyethylene glycol or vinylpyrrolidone-vinyl acetate copolymer or a mixture that consists of the above-mentioned substances is contained.

6. Pharmaceutical composition according to at least one of the above claims, wherein the melt extrusion is carried out without additional heat input.

7. Pharmaceutical composition according to at least one of claims 1 to 6 that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.

8. Pharmaceutical composition according to at least one of claims 1 to 6 that can be obtained by mixing 17- β -estradiol, polyvinylpyrrolidone and glycerol tribehenate and joint melt extrusion at 60°C.

9. Pharmaceutical composition according to at least one of claims 1 to 6 that can be obtained by mixing ethinylestradiol, polyvinylpyrrolidone and saccharose monopalmitate and joint melt extrusion at 60°C.

10. Process for the production of pharmaceutical compositions in which at least one active ingredient is mixed with at least one extrusion additive from the group of polyalcohols esterified with fatty acids, and the mixture that is thus obtained is then subjected to a joint melt extrusion.

11. Process according to claim 10, wherein the melt extrusion is carried out without heat input.

12. Process according to claim 10 or 11, wherein in addition, the extruded mixture is ground and further processed into pharmaceutical agents with additional pharmaceutically compatible adjuvants and additives.

13. Pharmaceutical agents that contain a pharmaceutical composition according to claim 1 together with additional pharmaceutically compatible adjuvants and additives.

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14. Use of polyalcohols that are esterified with fatty acids as extrusion additives for the production of pharmaceutical compositions.

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Fig. 1

Vergleich der Lösungsgeschwindigkeit von 17- β -E2 mit der von 17- β -E2 aus einem Schmelzextrudat und aus einer physikalischen Mischung

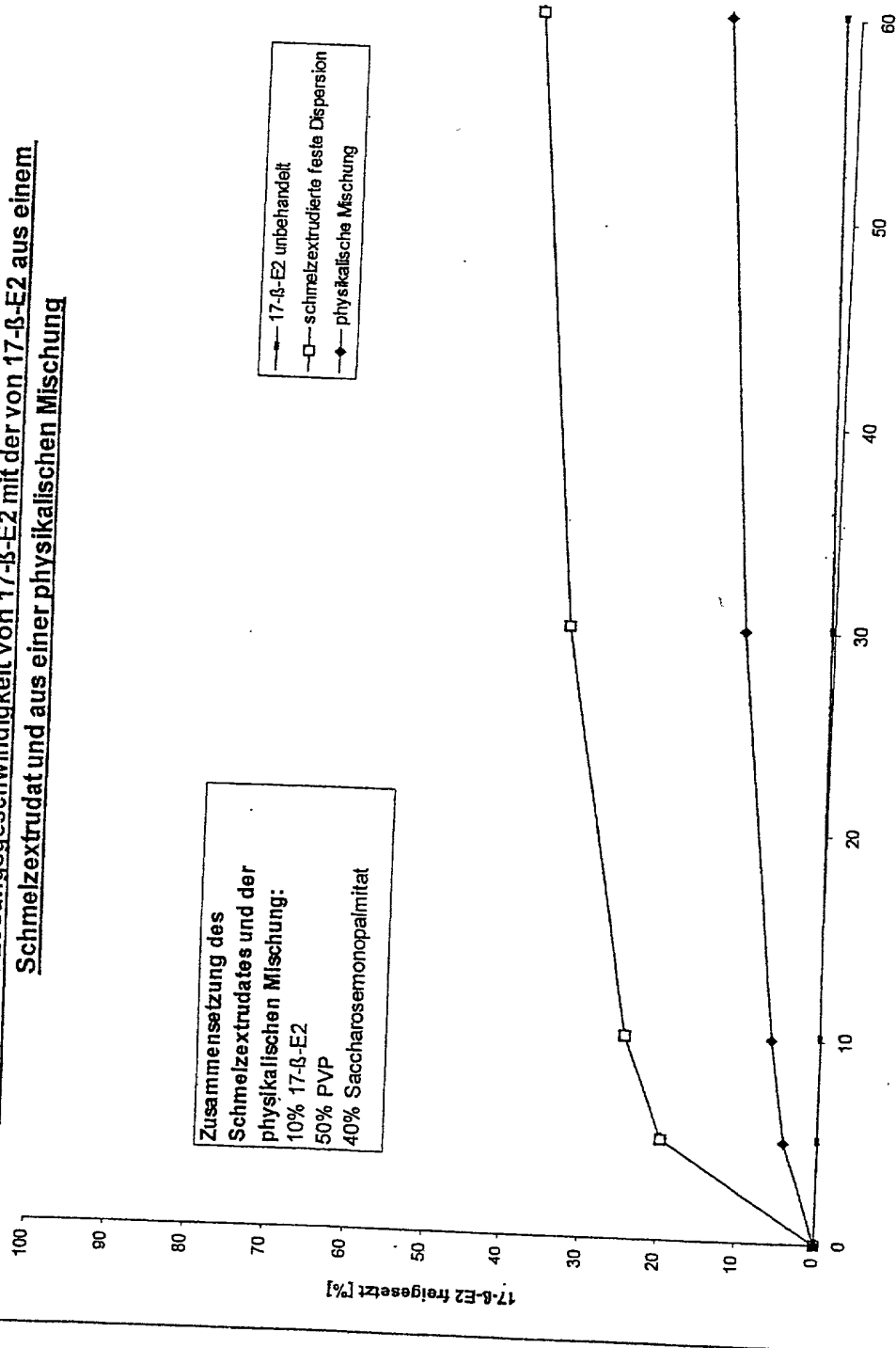
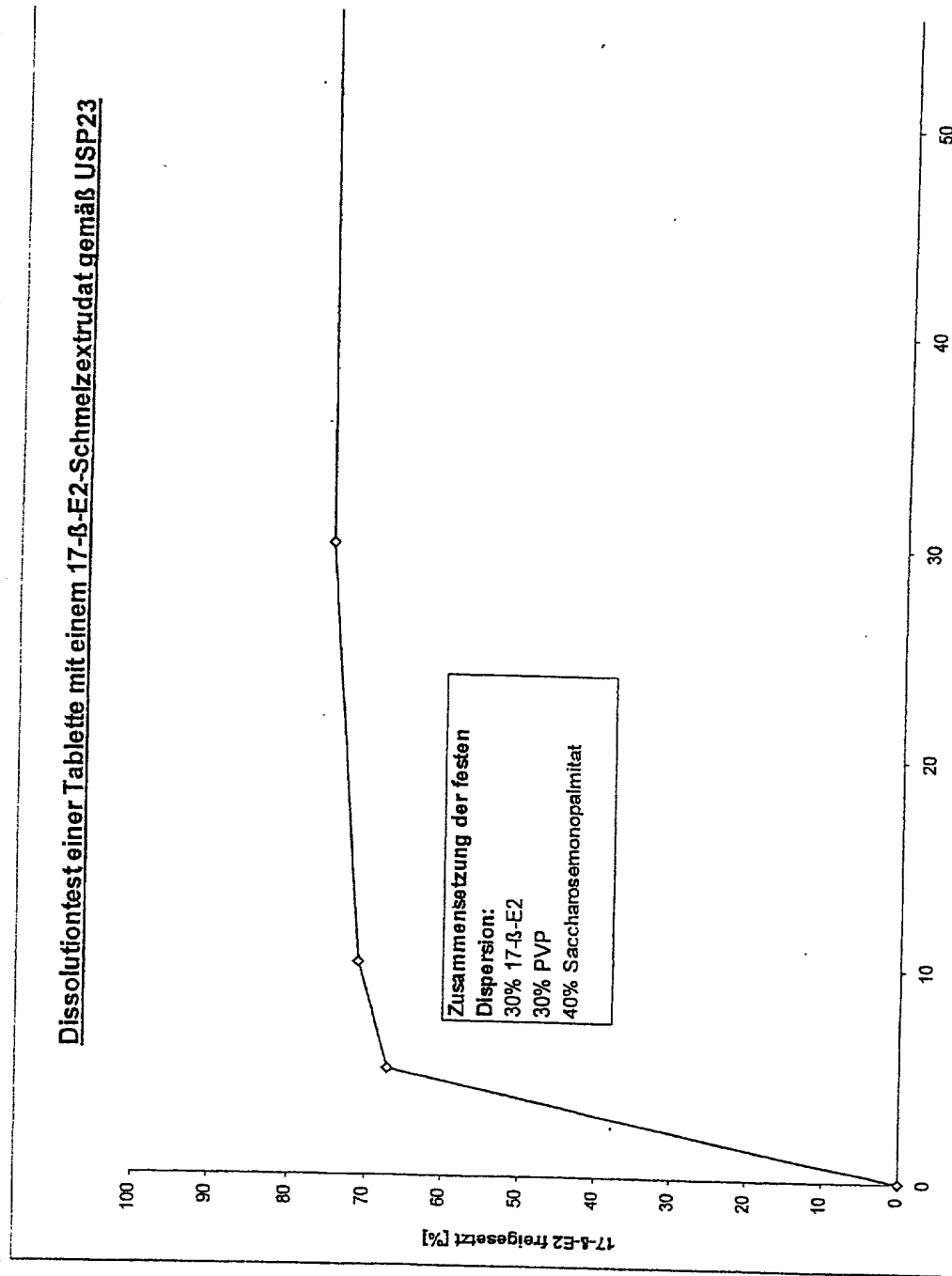


Fig. 2



DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PHARMACEUTICAL COMPOSITION CONTAINING AN EXTRUSION ADDITIVE

the specification of which

☐ is attached hereto

☒ was filed on 31 MARCH 2000 as United States Application Number or PCT International Application Number PCT/DE00/01028 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119

| APPLICATION NO. | COUNTRY | DAY/MONTH/YEAR FILED | PRIORITY CLAIMED |
|-----------------|---------|----------------------|------------------|
| 199 16 383.9 | GERMANY | 31 MARCH 1999 | YES |

☐ hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

| APPLICATION NUMBER | FILING DATE |
|--------------------|-------------|
| | |

☐ hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120

| APPLICATION NO. | FILING DATE | STATUS — PATENTED, PENDING, ABANDONED |
|-----------------|-------------|---------------------------------------|
| | | |

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E. McCarthy (46,044)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

| | |
|---|----------------------------|
| Full Name of sole or first inventor (given name, family name) | |
| Stefan HULSMANN | |
| Signature <i>[Signature]</i> | Date 26.02.02 |
| Residence Berlin, Germany DEX | Citizenship Germany |
| Post Office Address Saarbruckerstrasse 29, D-10405 Berlin Germany Schleiermacherstrasse 12, D-10961 Berlin Germany | |
| Full Name of additional joint inventor (given name, family name) Thomas BACKENSEELD | |
| Signature <i>[Signature]</i> | Date 25.02.02 |
| Residence Berlin, Germany DEX | Citizenship Germany |
| Post Office Address Eddastrasse 39, D-13127 Berlin Germany | |
| Full Name of additional joint inventor (given name, family name) | |
| Signature | Date |
| Residence | Citizenship |
| Post Office Address | |
| Full Name of additional joint inventor (given name, family name) | |
| Signature | Date |
| Residence | Citizenship |
| Post Office Address | |
| Full Name of additional joint inventor (given name, family name) | |
| Signature | Date |
| Residence | Citizenship |
| Post Office Address | |

☐ Additional joint inventors are named on separately numbered sheets attached hereto.